PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CPW/21822	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/GB2004/003209	International filing date *(day/month/year)* 23.07.2004	Priority date *(day/month/year)* 25.07.2003
International Patent Classification (IPC) or national classification and IPC A61K31/34, C07D307/87		
Applicant MEDITAB SPECIALITIES PVT.LTD. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 12 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.07.2005	23.11.2005
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003209

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-3, 8-15	as originally filed
4-7, 7a	received on 13.07.2005 with letter of 11.07.2005

Claims, Numbers

6(part), 7-13, 14(part), 41, 42	as originally filed
1-5, 6(part), 14(part), 15-40	received on 13.07.2005 with letter of 11.07.2005

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 37

because:

☒ the said international application, or the said claims Nos. 37 (method of medical treatment) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31, 38, 39
	No:	Claims	32-37, 40
Inventive step (IS)	Yes:	Claims	1-31, 38, 39
	No:	Claims	32-37, 40
Industrial applicability (IA)	Yes:	Claims	1-36,38-40
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The subject-matter as originally filed has been amended such that the subject-matter of original claims 15 and 19 has been incorporated into claims 1, 2, 6, 28 (= amended claim 26), 29 (= amended claim 27).

Re Item III

No unified criteria exist under the PCT for assessing the industrial applicability of the subject-matter of claim **37** as amended (a method of medical treatment). Hence it is not possible at this stage of the proceedings to give an opinion as to this claim's industrial applicability.

Re Item V

The following documents will be referred to:

D2: WO 2004/016602 A (NATCO PHARMA LIMITED) 26 February 2004
D3: GB-A-2 375 763 (MATRIX LABORATORIES LIMITED) 27 November 2002
D4: WO 01/68627 A (H LUNDBECK A/S) 20 September 2001
D5: EP-A-1 288 211 (SEKHSARIA CHEMICALS LTD) 5 March 2003

Processes for purifying citalopram involving the use of oxalic acid already exist in the art:

D2 discloses in step (e) on page 18 the step of washing an organic layer containing citalopram with 2 x 1000 ml of 10% oxalic acid. With the washing step in claim 1 being limited to an oxalic acid solution having a strength of 0.5 to 6%, the disclosure of D2 is not considered to be novelty-destroying. D3 also employs oxalic acid for purification purposes but not in the form of a dilute solution (cf. D3, claim 1, step (A)).

Whereas the processes according to the present application in amended form may be seen as novel with respect to the prior art, claims 32-37 and 40 directed to citalopram, a pharmaceutical formulation and a method of treating a disease are not to be regarded as novel as the prior art has already provided processes for purifying citalopram, processes which will provide citalopram in a purity achievable by the presently-claimed process. See, for example, D3. D4 and D5 would appear to produce products falling under the scope of the product claims of the present application. The use proposed for the purified citalopram in the

present application is no different to that of the prior art.

Summing up it would appear that claims 32-37 and 40 still lack novelty.

As for inventive step, D2 is to be regarded as the most relevant document as its teaching is not limited to oxalic acid - in claim 3, succinic acid is also mentioned as a possible acid. The list in claim 3 is not to be seen as exhaustive by means of the wording "such as".

However, the principle behind D2 is (as the applicant has pointed out in his submissions of 11 July 2005) different to that employed in claim 1 of the present application. In D2 the objective of adding the acid is to make a salt with the citalopram with the citalopram being further reacted with base to release the citalopram. The strength of acid employed in the process of present claim 1 does not enable the formation of a salt with the citalopram but is sufficient to convert impurities more basic than citalopram into salts which can then be removed. The optional second washing step according to claim 2 does follow the same principles as D2 in that the salt of the citalopram is produced which can then be separated from impurities more basic in nature than citalopram.

As a result the subject-matter of the present claims is not to be regarded as derivable from the prior art or obvious to the person skilled in art. An inventive step can therefore be acknowledged for the subject-matter of claims 1-31, 38 and 39. Lacking novelty, claims 32-37 and 40 correspondingly lack an inventive step.

Re Item VII.

Document D2 should be briefly discussed in the description (Rule 5.1(a)(ii) PCT.

Re Item VIII.

Claims 38-40 as amended are typical British-style claims which do not add anything to the claims which precede them. They make reference to the description which may not be allowed in certain regional phases.

The present invention describes a simple and novel process for the large-scale manufacture and purification of citalopram, escitalopram and their pharmaceutically acceptable salts without tedious and time-consuming disadvantages associated with prior art processes. More particularly, the present invention employs certain polybasic acids either in free form or as partial alkali metal salts having the capability of forming salts selectively with the impurities of citalopram and citalopram itself. This property of the polybasic acids either in free form or as partial alkali metal salts has advantageously been utilized by the present invention to purify citalopram or its enantiomers.

More particularly, there is provided by the present invention a process of purifying citalopram, either in racemic or enantiomeric form, which process comprises:

(i) providing a crude mixture comprising citalopram, either in racemic or enantiomeric form, dissolved in a water immiscible organic solvent, and which mixture also includes one or more citalopram derivatives which are present as citalopram impurities;

(ii) washing said crude mixture with at least one dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, so as to separate said citalopram from citalopram impurities present in said crude mixture, said solution having a strength in the range of 0.5% to 6%; and

(iii) where required converting citalopram free base, separated from citalopram impurities further to step (ii), to a pharmaceutically acceptable salt.

In a preferred embodiment, a process according to the present invention comprises initial washing of the crude mixture with at least one dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, so as to remove citalopram impurities from the crude mixture, and subsequently washing the residual crude mixture with at least one further dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, said further solution having a strength in the range of 4% to 25%, so as to separate citalopram, either in racemic or enantiomeric form, from the impurities remaining in the crude mixture, by extraction of citalopram, as a salt formed with the polybasic acid,

into an aqueous phase. The thus obtained aqueous extraction phase now contains citalopram as a salt of the polybasic acid, to which can subsequently be added a base, such as an alkali metal hydroxide, such as sodium or potassium hydroxide, in an amount sufficient to liberate citalopram free base and extracting the liberated citalopram into an organic solvent.

According to the above described preferred embodiment of the present invention, there is provided a process of purifying citalopram, either in racemic or enantiomeric form, which process comprises:

(i) providing a crude mixture comprising citalopram, either in racemic or enantiomeric form, dissolved in a water immiscible organic solvent, and which mixture also includes one or more citalopram derivatives which are present as citalopram impurities;

(ii) washing said crude mixture with at least one dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, so as to remove citalopram impurities from the crude mixture, said solution having a strength in the range of 0.5% to 6%;

(iii) washing the residual crude mixture obtained further to step (ii) with at least one further dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, said solution having a strength in the range of 4% to 25%, so as to separate said citalopram from impurities remaining in said residual crude mixture, by extraction of citalopram, as a salt formed with the polybasic acid, into an aqueous phase and optionally washing the resulting aqueous phase with an organic solvent;

(iv) adding a base to the aqueous phase in an amount sufficient to liberate citalopram free base and extracting the liberated citalopram into an organic solvent;

(v) optionally re-extracting citalopram free base from the organic extract obtained further to step (iv) by washing with at least one further dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, so as to extract citalopram, as a salt

formed with the polybasic acid, into an aqueous phase and adding thereto a base in an amount sufficient to liberate citalopram free base and further extracting the liberated citalopram into an organic solvent; and

(vi) where required converting the free base obtained further to step (iv) or (v) to a pharmaceutically acceptable salt thereof.

Typically, the water immiscible solvent employed in step (i) as defined above can be selected from the group consisting of toluene, ethyl acetate, hexane and methylene dichloride. Preferably the water immiscible solvent is toluene or ethyl acetate.

Typically the polybasic acid is selected from the group consisting of tartaric acid, oxalic acid, fumaric acid, citric acid and edetic acid, which can either be employed in free form, or as a partial alkali metal salt. A suitable alkali metal salt is the sodium salt. A preferred polybasic acid is edetic acid, which can if required be preferably employed as disodium edetate.

The initial stage of washing the crude mixture with at least one dilute aqueous solution of a polybasic acid, either in free form, or as a partial alkali metal salt, suitably removes impurities from the crude mixture having higher basicity compared to citalopram. Typically, therefore, the initial washing with at least one dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, can remove the following impurities if present in the crude mixture: 5- carboxamide citalopram, N-desmethyl citalopram, desfluoro citalopram, 4[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile and / or 5-formyl citalopram. The strength of a dilute aqueous solution of a polybasic acid, either in free form, or as a partial alkali metal salt, as employed in the initial washing stage of a process according to the present invention is in the range of 0.5% to 6%.

Further to removal of the above referred to impurities from the crude mixture, the residual organic crude mixture comprises citalopram, either in racemic or enantiomeric form, together with impurities less basic than citalopram. A subsequent washing stage so as to

separate citalopram, either in racemic or enantiomeric form, from the thus residual crude mixture, comprises washing the residual crude mixture containing citalopram, either in racemic or enantiomeric form, with at least one further dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, whereby citalopram as a salt formed with the polybasic acid is extracted into an aqueous phase. This extraction is normally done at ambient temperature, but can be done equally effectively at elevated temperatures, such as 40 to 80°C. It will be appreciated, therefore, that residual impurities having a basicity of less than citalopram, such as for example, descyano citalopram, 5-chloro citalopram and / or 5-bromo citalopram, are retained in the organic phase. The strength of a dilute aqueous solution of a polybasic acid, either in free form, or as a partial alkali metal salt, as employed in the subsequent washing stage of a process according to the present invention, is in the range of 4% to 25%.

The resulting aqueous phase now contains citalopram, either in racemic or enantiomeric form, as a salt with the polybasic acid. The aqueous phase can also be further purified by washing with an organic solvent as indicated above, such as toluene, ethyl acetate, hexane, methylene dichloride, or the like. During this washing of the aqueous phase with an organic solvent, such as toluene, it may be desirable for the aqueous phase to be further strengthened by adding small amounts of polybasic acid prior to the organic wash, as this can be more effective and loss of citalopram into the organic phase can be reduced.

A process according to the present invention preferably further comprises adding a base to the aqueous phase in an amount sufficient to liberate citalopram free base, and suitably the base comprises an aqueous alkali metal hydroxide solution, such as aqueous sodium hydroxide or potassium hydroxide. Typically, the liberated citalopram free base is then extracted from the aqueous phase into a water immiscible solvent, such as ethyl acetate. It may be desirable as indicated above to carry out a re-extraction process of the citalopram free base present in the resulting organic extract, by washing with at least one further dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, so as to extract citalopram, as a salt formed with the polybasic acid, into an aqueous phase and again adding thereto a base in an amount sufficient to liberate citalopram free base and

further extracting the liberated citalopram into an organic solvent. This re-extraction process can also help to remove less basic citalopram impurities.

The resulting citalopram free base can where required be converted to a pharmaceutically acceptable salt of citalopram, such as the hydrobromide, hydrochloride or oxalate. The

CLAIMS

1. A process of purifying citalopram, either in racemic or enantiomeric form, which process comprises:

(i) providing a crude mixture comprising citalopram, either in racemic or enantiomeric form, dissolved in a water immiscible organic solvent, and which mixture also includes one or more citalopram derivatives which are present as citalopram impurities;

(ii) washing said crude mixture with at least one dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, so as to separate said citalopram from citalopram impurities present in said crude mixture, said solution having a strength in the range of 0.5% to 6%; and

(iii) where required converting citalopram free base, separated from citalopram impurities further to step (ii), to a pharmaceutically acceptable salt.

2. A process according to claim 1, which comprises carrying out an initial washing of the crude mixture with at least one dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, so as to remove citalopram impurities from the crude mixture, and subsequently washing the residual crude mixture with at least one further dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, said further solution having a strength in the range of 4% to 25%, so as to separate citalopram, either in racemic or enantiomeric form, from the impurities remaining in the crude mixture, by extraction of citalopram, as a salt formed with the polybasic acid, into an aqueous phase.

3. A process according to claim 2, wherein the impurities removed from the crude mixture by the initial washing with said at least one dilute aqueous solution of a polybasic acid have a basicity of greater than the basicity of citalopram.

4. A process according to claim 3, wherein the impurities remaining in the crude mixture further to the initial washing with said at least one dilute aqueous solution of said polybasic acid have a basicity of less than the basicity of citalopram.

5. A process according to any of claims 2 to 4, wherein a base is added to the aqueous phase containing citalopram as a salt of the polybasic acid, in an amount sufficient to liberate citalopram free base which is then extracted into an organic solvent.

6. A process of purifying citalopram, either in racemic or enantiomeric form, which process comprises:

(i) providing a crude mixture comprising citalopram, either in racemic or enantiomeric form, dissolved in a water immiscible organic solvent, and which mixture also includes one or more citalopram derivatives which are present as citalopram impurities;

(ii) washing said crude mixture with at least one dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, so as to remove citalopram impurities from the crude mixture, said solution having a strength in the range of 0.5% to 6%;

(iii) washing the residual crude mixture obtained further to step (ii) with at least one further dilute aqueous solution of a polybasic acid, either in free form or as a partial alkali metal salt, said further solution having a strength in the range of 4% to 25%, so as to separate said citalopram from impurities remaining in said residual crude mixture, by extraction of citalopram, as a salt formed with the polybasic acid, into an aqueous phase and optionally washing the resulting aqueous phase with an organic solvent;

(iv) adding a base to the aqueous phase in an amount sufficient to liberate citalopram free base and extracting the liberated citalopram into an organic solvent;

(v) optionally re-extracting citalopram free base from the organic extract obtained further to step (iv) by washing with at least one further dilute aqueous solution of a polybasic acid,

either in free form or as a partial alkali metal salt, so as to extract citalopram, as a salt formed with the polybasic acid, into an aqueous phase and adding thereto a base in an

fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile and / or 5-formyl citalopram.

15. A process according to any of claims 2 to 14, wherein the subsequent washing separates citalopram from the residual crude mixture, whereby citalopram as a salt formed with disodium edetate is extracted into an aqueous phase.

16. A process according to any of claims 6 to 15, wherein the impurities remaining in the residual crude mixture subsequent to the initial washing have a basicity of less than citalopram.

17. A process according to claim 4 or 16, wherein the impurities remaining in the residual crude mixture subsequent to the initial washing are selected from the group consisting of descyano citalopram, 5-chloro citalopram and 5-bromo citalopram.

18. A process according to any of claims 2 to 17, wherein the subsequent washing is carried out at a temperature in the range of 40 to 80°C.

19. A process according to any of claims 5 to 18, wherein said base comprises an aqueous alkali metal hydroxide solution.

20. A process according to claim 19, wherein the base is aqueous sodium hydroxide or potassium hydroxide.

21. A process according to any of claims 5 to 20, wherein the liberated citalopram free base is extracted from the aqueous phase into ethyl acetate.

22. A process according to any of claims 1 to 21, which includes converting citalopram free base to a pharmaceutically acceptable salt of citalopram.

23. A process according to claim 22, wherein the pharmaceutically acceptable salt is selected from the group consisting of the hydrobromide, hydrochloride and oxalate.

24. A process of preparing citalopram, either in racemic or enantiomeric form, by ring closure of 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3(hydroxymethyl)-benzonitrile, dissolving the resulting citalopram, together with one or more citalopram derivatives which are present as citalopram impurities, in a water immiscible organic solvent so as to provide a crude mixture thereof, and subjecting the resulting crude mixture to a purification process according to any of claims 1 to 23.

25. A process of preparing citalopram, either in racemic or enantiomeric form, by conversion of 1-[3-(dimethylamino)propyl]-1-(4-flurophenyl)-5-bromo pthalane to the corresponding cyano derivative, namely citalopram, dissolving the resulting citalopram, together with one or more citalopram derivatives which are present as citalopram impurities, in a water immiscible organic solvent so as to provide a crude mixture thereof, and subjecting the resulting crude mixture to a purification process according to any of claims 1 to 23.

26. Use of at least one polybasic acid, either in free form or as a partial alkali metal salt, in the purification of citalopram, either in racemic or enantiomeric form, wherein said polybasic acid is present in a dilute aqueous solution having a strength in the range of 0.5% to 6%.

27. Use (i) of at least one polybasic acid, either in free form or as a partial alkali metal salt, so as to remove one or more citalopram impurities from a crude mixture including citalopram, either in racemic or enantiomeric form, wherein said polybasic acid is present in a dilute aqueous solution having a strength in the range of 0.5% to 6%, wherein said citalopram impurities comprise one or more citalopram derivatives having higher basicity compared to citalopram; in combination with use (ii) of at least one polybasic acid, either in free form or as a partial alkali metal salt, so as to separate citalopram, either in racemic or enantiomeric form, from the impurities remaining in the residual crude mixture obtained further to use (i), by extraction of citalopram, as a salt formed with the polybasic acid, into an aqueous phase, wherein said polybasic acid in use (ii) is present in a dilute aqueous solution having a strength in the range of 4% to 25%.

28. Use according to claim 26 or 27, wherein the polybasic acid is selected from the group consisting of tartaric acid, oxalic acid, fumaric acid, citric acid and edetic acid, which can either be employed in free form, or as a partial alkali metal salt.

29. Use according to claim 28, wherein the alkali metal salt is the sodium salt.

30. Use according to claim 28, wherein the polybasic acid is edetic acid.

31. Use according to claim 30, wherein said edetic acid is employed as disodium edetate.

32. Citalopram free base, or a pharmaceutically acceptable salt thereof, either in racemic or enantiomeric form, prepared by a process according to any of claims 1 to 25.

33. Citalopram according to claim 32, which includes less than about 0.1% citalopram derivatives present as citalopram impurities.

34. Citalopram according to claim 33, which is more than 99.7% w/w pure (peak area).

35. A pharmaceutical formulation comprising citalopram according to any of claims 32 to 34, together with a pharmaceutically acceptable carrier or excipient therefor.

36. Citalopram according to any of claims 32 to 34, for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of a serotonin reuptake inhibitor.

37. A method of treating a disease state prevented, ameliorated or eliminated by the administration of a serotonin reuptake inhibitor in a patient in need of such treatment, which method comprises administering to the patient an effective amount of citalopram according to any of claims 32 to 34.

38. A process of purifying citalopram, either in racemic or enantiomeric form, substantially as illustrated by the Examples.

39. A process of preparing citalopram, or a pharmaceutically acceptable salt thereof, either in racemic or enantiomeric form, substantially as illustrated by the Examples.

40. Citalopram prepared substantially as described in the Examples.